REMARKS

Claims 1-16, and 18-74 are pending and under examination with claims 66-69 having been withdrawn from consideration as being directed to a non-elected invention. Applicants reserve the right to pursue these claims in a later filed application claiming the benefit of the subject application. By the present communication, no claims have been added, canceled, or amended. Applicants have reviewed the Office Action mailed February 26, 2007, and respectfully traverse all grounds of rejection for the reasons that follow.

Rejections Under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 1-9, 11, 14, 15, 18-28, 30, 32-42, 44, 45, 48, 49, 51-60, 62, 63, and 70-74 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, *et al.* (*AICHE Journal* 42(5): 1996-2005 (1996); hereinafter "Hatzimanikatis"). Applicants respectfully maintain, for the reasons of record, that the claimed computer readable medium or media is unobvious over Hatzimanikatis.

As discussed in the previous response, to establish a *prima facie* case of obviousness, the Office must show that the prior art would have suggested the claimed invention to one of ordinary skill in the art and that it could have been carried out with a reasonable likelihood of success when viewed in the light of the prior art. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000), accord *In re Royka*, 180 USPQ 580 (C.C.P.A. 1974) (to establish *prima facie* obviousness, all claim limitations must be taught or suggested by the prior art); M.P.E.P. §2143.03.

Contrary to the assertion by the Office Action, Hatzimanikatis does not teach or suggest providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of said reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product, and wherein at least one of said reactions is a regulated reaction, as required by the instant claims. Hatzimanikatis states in the abstract that "[A] regulatory superstructure proposed contains all alternative regulatory structures that can be

considered for a given pathway" (emphasis added). As discussed in the previous response, Hatzimanikatis, at most, describes a mathematical framework for determining changes in regulatory structure and strength that should be considered to optimize a particular metabolic process (see page 1278, 2nd col., 3rd paragraph). The reference further states on page 1278, 1st col., 3rd paragraph:

> Modifying the regulatory characteristics of an enzyme is presently a much more difficult experimental challenge than changing the amount of enzyme present in the cell. Therefore, guidance as to what changes in regulation might be of greatest benefit to improve the network is important. To this end, a systematic, multilevel, multiparametric methodology for evolving effective control structures is needed. [emphasis added].

Hatzimanikatis indicates that it deals with a mathematical description of a metabolic pathway with a postulated number of regulatory loops and that the objective is to determine which of the regulatory loops should be retained (page 1279, 1st col., 1st complete paragraph). Hatzimanikatis further describes consideration of a "regulatory superstructure" in which "every metabolite in the system can potentially regulate any enzyme in that system" (page 1279, 1st col., 3rd complete paragraph; emphasis added). Such a "regulatory superstructure" is clearly a postulation of possible regulatory loops since "every metabolite" cannot regulate "any enzyme." Hatzimanikatis describes computational studies to determine regulatory loops that would provide a desired outcome, which can then be utilized "for evolving effective control structures" (page 1278, 1st col., 3rd paragraph). The theoretical approach is followed in order to find the optimal regulatory structure for maximization of phenylalanine selectivity in the microbial aromatic amino acid synthesis pathway (see abstract). For example, in Problem 1 described on page 1284, there are eight feedback inhibitory loops in the original regulatory structure of the aromatic amino acid synthesis pathway (Figure 1), which provides $2^8 = 256$ alternative regulatory structures (page 1284, 1st col., 4th complete paragraph). The reference indicates that inactivation of at least three loops and overexpression of three enzymes increased phenylalanine selectivity (page 1285, 1st col., 2nd complete paragraph). Hatzimanikatis concludes at page 1289, left column, final paragraph:

> The problem of designing the regulatory structures built around a given metabolic reaction network was formulated as a MILP optimization problem. A synthesis approach has been proposed which assumes that the metabolic pathway of interest has no regulation, and considers which regulatory structure optimizes the objective. [emphasis added]

Thus, it is clear that Hatzimanikatis describes designing regulatory structures, including regulatory loops that do not naturally occur in a metabolic pathway. However, Hatzimanikatis provides no teaching or suggestion of a computer readable medium or media having stored thereon computer-implemented instructions causing a processor to perform the steps that include providing a data structure relating a plurality of reactants to a plurality of reactions of a biochemical reaction network, wherein each of the reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product, and wherein at least one of the reactions is a regulated reaction, providing a constraint set for the plurality of reactions, wherein the constraint set comprises a variable constraint for the regulated reaction, and determining at least one flux distribution that minimizes or maximizes an objective function when the constraint set is applied to the data structure, wherein the at least one flux distribution determines a systemic property of the biochemical reaction network, and wherein the systemic property is dependent upon the flux through the regulated reaction. Thus, the claimed methods are not directed to finding a regulatory structure to optimize the objective based on the theoretical possibility that "every metabolite" can "potentially regulate any enzyme," as described in Hatzimanikatis. Furthermore, Applicants respectfully disagree with the assertion in the Office Action on page 15 that the claims read on the concepts in Hatzimanikatis. To the contrary, and as discussed above, Hatzimanikatis does not teach or suggest the claimed computer readable medium or media and methods. Accordingly, Applicants submit that the claimed methods are unobvious over Hatzimanikatis and respectfully request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 10, 12, 43, and 46 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, as applied to claims 1-9, 14-15, 18-28, 30, 32, 33, 34-42, 44, 45, 48, 49, 51-60, 62-63 and 70-74, and further in view of Grewal,

et al. (Protein Engineering 7:205-211(1994); hereinafter, "Grewal"). This rejection relies on Hatzimanikatis et al. as the primary reference. The arguments presented above with regard to Hatzimanikatis apply equally and are incorporated here. Thus, Applicants have set forth the deficiencies of Hatzimanikatis, which are not cured by viewing Hatzimanikatis in combination with Grewal. Accordingly, Applicants respectfully submit that the deficiencies of Hatzimanikatis are not cured by viewing Hatzimanikatis in combination with Grewal, and request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 31, 64, and 65 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, as applied to claims 1-9, 14-15, 18-28, 30, 32, 33, 34-42, 44, 45, 48, 49, 51-60, 62-63 and 70-74, and further in view of Liao, *et al.* (Biotechnology and Bioengineering 52:129-140 (1996); hereinafter, "Liao"). This rejection relies on Hatzimanikatis et al. as the primary reference. The arguments presented above with regard to Hatzimanikatis apply equally and are incorporated here. Thus, Applicants have set forth the deficiencies of Hatzimanikatis, which are not cured by viewing Hatzimanikatis in combination with Liao. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis in view of Liao, and request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 16 and 50 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, as applied to claims 1-9, 14-15, 18-28, 30, 32, 33, 34-42, 44, 45, 48, 49, 51-60, 62-63 and 70-74, and further in view of Kim, *et al.* (U.S. 2002/00087275; hereinafter, "Kim"). This rejection relies on Hatzimanikatis et al. as the primary reference. The arguments presented above with regard to Hatzimanikatis apply equally and are incorporated here. Thus, Applicants have set forth the deficiencies of Hatzimanikatis, which are not cured by viewing Hatzimanikatis in combination with Kim. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis in view of Kim, and request withdrawal of the rejection.

Applicants respectfully traverse the rejection of claims 13 and 47 under 35 U.S.C. §103(a) as allegedly being obvious over Hatzimanikatis, as applied to claims 1-9, 14-15, 18-28, 30, 32, 33, 34-42, 44, 45, 48, 49, 51-60, 62-63 and 70-74, and further in view of Vissing, *et al.* (Neurology 47:766-771 (1996); hereinafter, "Vissing"). This rejection relies on Hatzimanikatis et al. as the primary reference. The arguments presented above with regard to Hatzimanikatis apply equally and are incorporated here. Thus, Applicants have set forth the deficiencies of Hatzimanikatis, which are not cured by viewing Hatzimanikatis in combination with Vissing. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis in view of Vissing, and request withdrawal of the rejection.

CONCLUSION

In summary, for the reasons set forth herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge $1,005.00 as payment for the Petition for the Three-Month Extension of Time fee ($555.00), the Information Disclosure Statement fee ($180.00), and the Notice of Appeal fee ($270.00) to Deposit Account No. 07-1896. Additionally, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

Date: January 16, 2009

Antony M. Novom, J.D.
Reg. No. 45,517
Telephone No.: (858) 638-6641
Facsimile No.: (858) 677-1465

DLA PIPER LLP (US)
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO CUSTOMER NUMBER 28213